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July 2, 2002



Dockets Management Branch
(HFA-305)
Food and Drug Administration
5630 Fishers Lane – Room 1061
Rockville, MD 20652

Docket Number: 02N-0152

Dear Sir or Madam:

As President of Baylor College of Medicine and Physician-in-Chief of Texas Children's Hospital, the largest children's hospital in the United States, I welcome the opportunity to comment on the relationship between the 1998 Pediatric Rule and the Best Pharmaceuticals for Children Act (P.L. 107-109). Securing safe and appropriate drugs for use by children has had a long and laborious history. Significant progress toward pediatric drug studies and labeling has been made over the last five years but as the March 2002 proposal by the FDA to suspend the Pediatric Rule indicates, children are at risk of losing the ground we have fought so hard to secure for them.

The Pediatric Rule must be preserved and enhanced. It is an essential tool in ensuring that children have the quality and quantity of drugs they need. The Pediatric Rule makes medications for children a certainty, not an option. We can not overstate the importance of having the Pediatric Rule permanently in place as a therapeutic foundation for children.

When FDA issued the Pediatric Rule in 1998, they identified a number of gaps in the pediatric provision of the Food and Drug Administration Modernization Act (FDAMA) (P.L. 105-115). Several of those gaps were addressed with the passage of the reauthorization of the pediatric provision through the BPCA however, gaps remain. For example, despite language in BPCA to encourage drug studies for neonate or young children, BPCA will likely fall short of realizing that important goal.

The FDA has requested comments on several specific questions related to the relationship between the Pediatric Rule and the Best Pharmaceuticals for Children Act (BPCA). Let me begin with several general comments and recommendations related to both the Pediatric Rule and the BPCA:

**GENERAL COMMENTS** 02N-0152 C 21

- **All components of the current 1998 Pediatric Rule must remain in place. The Rule has proved successful in securing pediatric studies for new drugs coming onto the market and for drugs that are seeking a new labeled indication. While FDA has not yet invoked provisions related to section 201, it remains a critical piece to ensuring that children have appropriate drugs available for their use.**

  Securing properly studied medicines for children must not be left to chance.

While the BPCA provides two possible avenues to get off-patent and a narrowly defined number of on-patent drugs studied (i.e., through the Research Fund and the NIH Foundation) both approaches must rely on unpredictable streams of funding -- either through the Congress or through voluntary contributions from the pharmaceutical industry or other private funders.

Section 201 of the Pediatric Rule would require a manufacturer to submit an application containing pediatric study data, which may include dosage and administration in some or all pediatric subpopulations as well as formulations for those pediatric populations. This provision must remain in place.

- **Every pediatric study requested through BPCA or required by the Pediatric Rule must incorporate and reflect the spirit and intent of the ethical standards articulated in Subpart D (citation needed).**

- **In assessing whether an adult indication occurs in children, FDA should consider the pathophysiology of disease in children vs adults, metabolic pathway, and mechanism of action of the drug to decide appropriateness and necessity of pediatric studies.** FDA should determine if uses, beside the approved indication, might deserve study. The determination could be based on severity and incidence of illness and prevalence of use for the potential indication/s in children. (e.g., a drug for systemic hypertension in adults may be useful for pulmonary hypertension in neonates; a prostaglandian synthesis inhibitor for pain in adults may be useful for patent ductus arterosia in neonates; sleep disorders in infants and young children are quite different than sleep disorders in middle age adults and the same is true for gastroesophogeal reflux disease.).

- **There should be a <u>single</u> written request issued through BPCA that encompasses both off-label indications that need pediatric studies <u>AND</u> labeled indications that need pediatric studies. What is being sought is the most comprehensive pediatric use information for a particular drug – regardless of whether the indications to be studied are currently off-label or labeled. By having two separate written requests, the risk of a company rejecting a written request for a particular category is greater (e.g., an off-label use study may be more complicated or expensive to do and may influence whether a company chooses to accept the FDA's written request for those studies).**

**<u>SPECIFIC RESPONSES:</u>**

***What mechanisms, if any, may be necessary to augment the programs described in the BPCA and what present authorities, if any, are perhaps now redundant because of the BPCA?***

We must always keep in mind that BPCA is time-limited and subject to continuation by the Congress. Those facts speak directly to the need to ensure that the Pediatric Rule remains in place. Retiring or relaxing any authorities currently in the Pediatric Rule is inappropriate and would be to the detriment of children.

- It is necessary for FDA to establish (or expand an existing mechanism) a means to report the outcome data of all pediatric studies either requested through BPCA or required by the Pediatric Rule. All studies, both positive and negative, even if they do not yield labeling should be available in the public domain.

***What changes to the pediatric rule, if any, would be necessary to integrate the BPCA and the pediatric rule more effectively?***

- **The Pediatric Rule should apply to all labeled and potential indications as well as new indications**. FDA should consider the pathophysiology of disease, metabolic pathway, and mechanism of action of the drug to decide appropriateness and necessity of pediatric studies. If a company submits a supplemental indication to the FDA, it invokes the Pediatric Rule. It is important that appropriate pediatric studies be conducted for that new use; and if the current label lacks appropriate pediatric use information (e.g., for neonates) the FDA should also include in their requirement for pediatric studies of the new indication, any pediatric studies that may be needed for the currently labeled indications.

- **The rule should apply to child specific indications that may not exist, or exist to a minimum degree in the adult population**. For example, a drug that is approved for adult schizophrenia may have its greatest use in young children for treatment for ADHD.

***How would the criteria used by NIH and FDA under section 3 of the BPCA to request studies of already approved drugs relate to the standards promulgated in the pediatric rule and described in 21 CFR 201.23, 314.55, and 601.27 for requiring pediatric labeling for certain drugs and biological products? Which criteria are more appropriate for determining when studies are conducted?***

Study criteria: There are differing criteria for invoking either the BPCA and the Pediatric Rule as it relates to requesting or requiring pediatric studies. The BPCA uses a broad "may produce health benefits" standard. However, the Pediatric Rule states that if the product is likely to be used in a substantial number of pediatric patients (50,000) or would provide a "meaningful therapeutic benefit to pediatric patients over existing treatments" then drugs and biological products may be required to be studied for safety and effectiveness in pediatric populations.

*Recommendation*: Ideally, children would benefit by having the broader definition of "may produce health benefits" apply to the Pediatric Rule because that would capture more drugs and biologic products for their use.

Labeling Process: The Pediatric Rule states it may require a manufacturer to submit a supplemental application if the label does not include adequate information to support safe and effective use in pediatric populations. The dosing and administration in some or all pediatric populations (including neonates, infants, children and adolescents,) may be required, as well as pediatric formulations.

The Pediatric Rule lays out a process by which FDA will notify the manufacturer of its intent to require pediatric safety and effectiveness studies. There is an opportunity for a written response by the manufacturer and a meeting with FDA, which may include an advisory committee meeting. Then, FDA may provide a letter to the manufacturer of its intent to require pediatric studies. If a manufacturer fails to submit the supplemental application with the pediatric study information within the time specified by FDA, the drug product may be considered misbranded.

In the BPCA, the process for requesting pediatric studies of already marketed drugs and securing labeling is similar, though more specific:

- FDA issues a written request for pediatric studies to the manufacturer.

- BPCA designates pediatric drugs as "priority supplements" which triggers a goal of 6 months for the FDA to review pediatric labeling supplements submitted by the company;
- Within 180 days (6 months) from a company's submission of the pediatric studies report, the FDA must request whatever labeling change determined appropriate. Within that same 6 month period, if the company disagrees with FDA's recommendations for labeling changes, then FDA must immediately refer the matter to the FDA Pediatric Advisory Subcommittee.
- Within 90 days (3 months) the Pediatric Advisory Subcommittee must review the pediatric study reports and make a recommendation to the FDA Commissioner as to appropriate labeling changes;
- Within 30 days (1 month), the FDA Commissioner must consider the recommendations of the Subcommittee and make a final request to the company for a labeling change.
- If the company does not agree within 30 days (1 month) to this labeling change request, then the Commissioner may deem the drug misbranded.

*Recommendation*: The Pediatric Rule should adopt the process outlined in the BPCA for labeling drugs and biologics.

***What provisions, if any, of the BPCA could apply to biological products regulated under section 351 of the Public Health Service Act?***

No provision of BPCA applies specifically to biological products since the legislation focuses on drugs covered by the Food, Drug and Cosmetic Act (FDCA). While BPCA amends Part B of title IV of the Public Health Service Act (42 USC 284 et seq.) to establish a new "Research Fund for the Study of Drugs" (Section 409I of PL 107-109), the law limits drugs to be studied under the new Research Fund to those covered under the FDCA.

It should be noted that CBER regulates a small number of drug products that are subject to section 505. These products would be eligible for pediatric exclusivity if the other statutory conditions are met. Biological products that are subject to the Public Health Service Act are not eligible for pediatric exclusivity, even if they have orphan exclusivity or other patent protection.

*Summary statement*: Some of the most innovative new therapies now and in the future are biological products, which are not covered under BPCA. The Pediatric Rule is the only mechanism that ensures that biological products will be studied and available for children. Therefore, it is essential that the Pediatric Rule remain in place.

***How does the provision in section 3 of the BPCA providing for the recommendation for a formulation change relate to the pediatric rule provision stating that in certain cases a sponsor may be required to develop a pediatric formulation? Should pediatric formulations be required in certain cases?***

Appropriate formulations are an essential component of medications for the pediatric population and should be required in certain cases. Depending upon the age group, it may be necessary to develop one or more formulations (e.g., neonates, infants, children and adolescents). Both route of administration and taste must be taken into consideration for each medication.

Clearly Congress intended that formulations be a requisite part of the written request developed by FDA. There are several areas within the BPCA where congressional intent for formulations is both implicit and explicit.

1) Section 3 of BPCA includes a new provision [Sec. 409I] which requires NIH to develop and prioritize a list of off- and certain on-patent drugs. In developing the list, Congress requires the Secretary to consider a number of issues related to the drug, including "whether reformulation of the drug is necessary [Sec. 409I(a)(1)(D)]." Because the prioritized list of drugs includes certain on-patent drugs [Section 505A(d)(4)(B)(I)], it is clear that Congress intends reformulation to be a consideration for all on-patent drugs, since every on-patent drug has the possibility of appearing on the priority list.

2) Congress placed a strong emphasis on securing neonate studies of drugs. It is a fact that neonates need appropriate formulations for their use; therefore, formulations are intended to be an integral and requisite part of the BPCA:

   - When defining 'pediatric studies,' BPCA identified neonates as a specific population to be studied, if appropriate (Section 7).

   - BPCA specifically requires the Comptroller General of the United States to report to Congress on the efforts made by the Secretary of HHS to increase the number of studies conducted in neonates as well as efforts made to encourage the conduct of appropriate studies in neonates by companies with products that have sufficient safety and other information to make the conduct of studies ethical and safe.

BPCA limits its reference to "recommendation" for formulation changes only to studies completed under public contract [Sec 409I (c)(12)]. This provision was included to acknowledge that once a formulation is developed in the study phase, while it may be necessary to manufacture that formulation, it may not always be possible to scale up the formulation for distribution to the general public.

Similarly, while the Pediatric Rule requires that appropriate formulations for the age group(s) for which the drug will be studied, there is a provision that allows a waiver to be granted if "the applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for that age group have failed." (section 201.23, 601.27 and 314.55).

Thank you for your consideration of these comments.

Sincerely,

Ralph D. Feigin, M.D.

RDF:cb